Summation

In normal man, insulin secretion is constantly modulated by the state of nutrition, by the hormonal milieu and by autonomic impulses. The ingestion of nutrients, principally carbohydrate and protein, produces intestinal hormonal signals which prime and initiate insulin release by the beta cell. The interaction of glucose with a specific beta cell receptor augments or may separately induce the release of preformed insulin. This sequence involves the cyclic AMP system, beta adrenergic receptors and ions, principally calcium. Subsequent glucose metabolism within the beta cell provides energy for the further synthesis and release of insulin. The synthesis of insulin involves the formation of a precursor, proinsulin.

Defects or excesses of individual components in this complex integrated system can account for abnormalities in glucose tolerance or insulin secretion such as are seen, for example, in obesity, pheochromocytoma or acromegaly. In juvenile diabetes, the capacity for insulin secretion in response to any stimulus is almost totally abolished, though basal insulin levels remain essentially normal. In maturity onset diabetes, the capacity to secrete insulin in response to a stimulus remains, but the response is qualitatively or quantitatively diminished. This diminution is due to either a defect in the signal or the ability of the beta cell to perceive and act on that signal, or to peripheral antagonists of the biological actions of insulin.

New Developments in Diabetes Obesity and Insulin Resistance

GEORGE A. BRAY, MD*

HUMAN OBESITY is accompanied by increased levels of insulin. This was first suggested by the finding of hypertrophied beta cells in the islets of Langerhans in 13 of 19 obese patients at autopsy[126] and by the abnormalities in glucose tolerance which occur in many corpulent persons.[127-131] With the development of a radioimmunoassay for the detection of insulin, it became possible to document the increased concentrations of insulin in obesity.[28,132] It is now generally agreed that the fasting level of immuno-reactive insulin is higher in the serum of obese patients than of lean subjects.[133-136] Of importance is the fact that the insulin levels are correlated with body fat. This is illustrated by the data of Bagdade and his collaborators where a positive correlation between the level of insulin and the percentage of excess weight was readily demonstrable (Chart 1). With weight reduction, fasting levels of insulin returned toward normal.[36,137]

In addition to the increased fasting levels of insulin which accompany obesity, obese persons have a greater rise in insulin than do normal persons in response to many provocative agents. Thus, the administration of glucose to adults[133-141] or children,[142-145] or the administration of L-leucine,[146] of glucagon[147] or of tolbutamide,[148] is accompanied by a pronounced hyperinsulinemia in the obese patient which is substantially greater than is observed in normal people. If the increase in insulin during the various provocative tests is expressed as a percentage increase over basal concentrations of insulin, however, there is little or no difference in response between obese and lean persons.[35] Hence the magnitude of the insulin response in overweight persons is related primarily to the higher level of basal insulin in such persons. Concentrations of plasma insulin in fasting obese subjects are often elevated without change in the levels of circulating glucose.[136] These observations raise two important questions: (1) By what mechanism does obesity produce hyperinsulinemia; and (2) By what mechanism does the body prevent a drop in glucose in the face of increased circulating levels of insulin?

Insulin Secretion. Several possible mechanisms can be invoked to explain the hyperinsulinemia of obesity. The first is that the insulin measured by immunological methods is not biologically active and that in reality neither the turnover nor the production of glucose or of insulin is altered. This possibility received support following the discovery of proinsulin.[32] The work of Steiner and his collaborators has shown that the biosynthesis of insulin in the pancreatic beta cell is initiated by the production of a single-stranded proinsulin molecule. The conversion of proinsulin to insulin involves cleavage and removal of a connecting fragment (C-peptide) from the single-stranded proinsulin molecule with the production of a double-stranded molecule of insulin. The immunological properties of proinsulin are similar to those

*Associate Chief of Metabolism, Division of Endocrinology, Harbor General Hospital; Professor of Medicine, UCLA School of Medicine.

TABLE 7.—*Change with Obesity of Stimuli Which Enchance Insulin Secretion*

Stimuli for Insulin Secretion	*Changes in Obesity*
1. Metabolites	
Glucose	Normal or increased
FFA	Increased
Ketones	Normal
L-leucine	Increased
Ca	Normal
2. Gut Factors	?
3. Neural Factors	
Sympathetic	?
Parasympathetic	?
4. Hormones	
Glucagon	Decreased
Growth Hormone	Decreased
Cortisol	Normal or slightly decreased
Thyroxine	Normal

of native insulin, while the biological activity of the promolecule is only 1 to 2 percent of that of native insulin.[32]

This disparity between biological and immunochemical activities of insulin and proinsulin could provide an explanation for the hyperinsulinemia of obesity. This possibility has been tested, and proinsulin has been found to comprise a similar fraction of total circulating insulin in lean and in obese subjects. (See Chart 2.) The percentage of proinsulin is shown by the solid bars and the glucose and insulin in the upper panels of each pair. Glucose tolerance tests for three lean persons are shown in the upper three pairs of panels of the chart and for three obese persons in the lower three pairs of panels. Although the rise in total insulin is greater in several of the obese subjects, there is little or no difference in the fraction of proinsulin which is produced during glucose stimulation of the pancreatic beta cell.[149]

A decreased rate of insulin turnover could also explain the higher levels of basal insulin. At present, few data are available on the turnover of insulin in obesity. Insulin degradation has been examined in experimental animals, however, and is not altered either *in vivo* or *in vitro*. That is, the removal of insulin is related to the circulating concentration of this hormone.[150] As the concentration of insulin in the circulation rises, the quantity removed also rises because turnover rate remains constant. For a reduction in peripheral degradation to produce a rise in circulating levels of insulin would require that secretion rate remained normal and did not fall with a decline in peripheral turnover. The evidence, although scanty, would suggest that a significant reduction in the clearance of insulin is not the underlying mechanism for the rise in concentration of the fasting insulin in obese subjects.[135]

If the increased basal levels of insulin reflect enhanced secretion of insulin, then the question becomes: By what mechanism is the secretion of insulin augmented? Currently available data indicate that insulin secretion is controlled by a number of humoral and neural signals. These have been reviewed in detail previously. Since the increased basal level in insulin is the predominant effect of obesity, Table 7 has been constructed to compare the concentrations of various humoral and neural signals in the basal state and the response of these stimuli during the infusion. The concentration of glucose, a prime stimulus for insulin secretion, is either normal or modestly increased in obesity. L-arginine, glucagon, growth hormone and calcium, all of which can stimulate insulin secretion, are normal or reduced in obesity.[27,30,31,135,151] Only L-leucine, among secretogogues for insulin, is increased in concentration in the circulation of corpulent people. The elevated levels of this amino acid in plasma led Felig et al[152] to suggest that this amino acid may play an important role in the high levels of insulin found in obesity.

The role of neural signals in the control of insulin levels in obesity is as yet unexplored. However, recent evidence indicates that α-receptor blockage with phentolamine will enhance basal insulin levels in normal subjects while β-receptor blockade will lower it.[83,153] From this summary, it is evident that at present only the increased level of L-leucine provides an explanation for the hyperinsulinemia of the obese state. As will be noted later, however, increased body weight induced in normal persons by a period of enforced overeating also raises the concentration of L-leucine, which suggests that the rise in the concentration of this amino acid is a consequence of obesity rather than a primary cause of the hyperinsulinemia.[154] If this is so, then no satisfactory explanation exists for the hyperinsulinemia of obesity.

Insulin Resistance. Obese persons have normal concentrations of glucose in the presence of high levels of circulating insulin, suggesting resistance to the peripheral actions of insulin. The studies of Rabinowitz and Zierler,[132] using a technique for perfusing the human forearm, were among the earliest studies to suggest resistance to insulin. With their technique, blood specimens from the brachial artery and from superficial and deep venous channels could be collected simultane-

ously. The deep venous channels drained primarily muscle and the superficial veins drained mainly the fat depots. In their study, the obese subjects were approximately 20 percent above normal weight. This degree of excess weight, however, represents nearly a doubling of the total body fat. Before insulin was given, the uptake of glucose by muscles in the forearm was similar in lean and obese subjects. During a 26-minute intra-arterial infusion of insulin, however, the obese subjects showed smaller effects on the metabolism of glucose than did the lean subjects. From their studies, Rabinowitz and Zierler concluded that both muscle and adipose tissue of obese subjects were resistant to the actions of insulin.[132]

Salans, Knittle and Hirsch[155] used a second approach to examine insulin resistance in obesity. Their technique consisted of incubating an aspirated biopsy specimen of adipose tissue *in vitro* before and after weight loss. The conversion of radioactivity from glucose-1-^{14}C to $^{14}CO_2$ in the presence or absence of insulin was used to measure the effects of this hormone. The difference between insulin-stimulated and basal levels of glucose oxidation was greater after weight loss than before. The difference was due largely to a decline in the basal oxidation of glucose to CO_2 Maximal glucose oxidation in the presence of insulin showed little change with weight loss.

These investigators interpreted their data as indicating that small adipocytes were more sensitive to insulin. An equally valid interpretation would suggest that glucose metabolism without hormones was enhanced by the smaller adipocytes obtained after weight loss, but that the effects of insulin were not changed. Whichever interpretation one takes, the possibility that enlarged adipocytes were the mechanism for resistance to insulin has stimulated numerous studies to examine this hypothesis. Among the factors that have been shown to control the responsiveness to insulin in adipose tissue are (1) the size of the adipocytes,[156] (2) the total caloric intake,[157] (3) the fraction of carbohydrate in the diet before testing the effects of insulin[37,154] and (4) the presence of functional beta cells.[158]

Adipose tissue of growing animals is more sensitive to the effects of insulin than adipose tissue of adult animals.[156,159] However, large adipocytes from older animals can be made as sensitive as small adipocytes from young animals if the old animals are first fasted and then allowed to reaccumulate fat rapidly.[156,159] Thus, enlargement of adipocytes does not necessarily increase their resistance to insulin. A similar conclusion was reached in studies with adipose cells from obese humans.[157] The sensitivity of isolated adipocytes to insulin could be enhanced by overfeeding with a high carbohydrate diet containing 5,000 calories for a period of two weeks. Similarly, brief periods of caloric restriction to 900 calories a day abolished the responses to insulin, indicating critical importance of knowing the total caloric intake before assessing the effects of this hormone.[157]

The composition of the diet is another factor modulating the sensitivity to insulin. There is now convincing evidence that the magnitude of the response of this hormone in small and large adipocytes is a function of the carbohydrate intake.[37,154] The stimulation of glucose oxidation by insulin *in vitro* is enhanced in adipose tissue obtained from rats fed a high carbohydrate diet. A similar effect occurs in human fat. When adipose tissue is obtained from lean human subjects on a high carbohydrate diet and incubated with insulin, more glucose is oxidized to CO_2 than with fat from the same subjects after feeding a low carbohydrate diet.[154]

Intact pancreatic beta cells are a fourth factor involved in regulating the resistance to insulin. Resistance to the hypoglycemic effects of exogenous insulin is a hallmark of the genetically obese mouse (ob/ob).[19] Destruction of the pancreatic beta cells in these animals by injecting alloxan, restores the hypoglycemic effect of exogenous insulin. This occurs without a change in body weight and without a change in size of the adipocytes. These studies indicate that some factor from the pancreas, either endogenous insulin or some other factor, is an essential element in the insulin resistance of these mice.[158]

Although the size of the adipocyte is one factor in determining the resistance to insulin, it appears that total intake of carbohydrates or calories or both, is at least as important. It seems unlikely that resistance of the adipocyte to the action of insulin can provide the entire explanation for impaired effectiveness of this hormone in obese subjects, since the quantity of glucose metabolized by adipose tissue accounts for only a small fraction of total glucose metabolism. Pronounced changes in resistance of adipose tissue alone could not explain alterations in the resistance to the metabolism of glucose. In addition, the studies of Rabinowitz and Zierler[132] in obese subjects indicate that

TABLE 8.—*Some Conclusions from the Vermont Study of Experimental Obesity in Man*

Parameters	*Responses*
Weight Gain	Difficult
Weight Loss	Easy—Returned to Normal
Insulin	
Basal	↑
After Glucose	↑
Oral Glucose Tolerance	Impaired
Intravenous Glucose Tolerance	Impaired
Cholesterol	↑
Triglycerides	↑
Free Fatty Acids	↓ or Unchanged
Cortisol	
Concentration	↓
Secretory Rate	↑
Growth Hormone Secretion	↓
Adipose Tissue	
Cell Size	↑
Number of Cells	Unchanged
Response to Insulin *in vitro*	↓
Lipogenesis (^{14}pyruvate-^{14}C→FA)	↓
Lipolysis	↑
Forearm	
Effect of Insulin	↓
Serum Leucine, Valine	↑

muscle is also resistant to the action of insulin.

The experiments of Sims and his colleagues at the University of Vermont[154] have provided a number of additional insights into the role of diet, adipose tissue and muscle metabolism in the development of insulin resistance in experimental obesity (Table 8). These investigators asked the following question: What happens to the endocrine profile of obesity when lean subjects gain weight by a period of self-induced overeating? For their studies, four groups from the Vermont Penal Institution and one group at the Clinical Research Center volunteered to overeat and gain between 15 and 20 percent of the initial body weight. All subjects in these studies were lean and none had been previously overweight, nor did they have a family history of diabetes. The initial studies were performed while the volunteers ate a diet calculated to maintain body weight. This was followed by several months of increased food intake. Body composition was calculated initially and at the end of the studies. Following the accretion of weight, the subjects submitted to the same tests that they had undergone at the beginning of the study.

The results of these studies are summarized in Table 11 under a number of headings. For the present purpose, we will examine the contribution from the study of insulin level and adipose tissue. After weight gain, regardless of the type of diet used to increase body weight, the basal levels of insulin were increased as was the rise following the administration of glucose. Thus, hyperinsulinemia can be induced in normal subjects by weight gain produced by overeating. Hence, at least some components of the increase in basal insulin in obesity is a consequence of the enhanced weight of these subjects. This concept is consistent with the studies of insulin levels during weight loss when insulin returns toward normal.[137]

The studies of adipose tissue were performed in two different studies. The first utilized aspiration biopsy material before and after weight gain when the volunteers were eating a mixed diet. The second used specimens of fat obtained surgically before and then after weight gain when the volunteers were eating a controlled diet with varying carbohydrate level. In this latter study, one diet contained 300 grams and the other 100 grams of carbohydrate per square meter of body surface. With this experimental design, it was possible to examine the effects of dietary carbohydrate and the size of fat cells on the response to insulin. The utilization of glucose by adipose tissue in the absence of insulin was significantly increased in the enlarged adipocytes. This is the mirror image of observations on weight loss, where basal level of glucose utilization declined as adipocyte cells decreased in size. After a period of weight gain, the increment in radioactivity converted from glucose-1-^{14}C to $^{14}CO_2$ in response to insulin was diminished. The response of adipose tissue to insulin was enhanced on the high carbohydrate diet. Resistance to the action of insulin was also demonstrated in studies on using the perfused forearm. After weight gain, the intra-arterial infusion of insulin showed a pattern similar to that observed by Rabinowitz and Zierler[154] in their studies of people with spontaneous obesity. From these studies, Sims concluded that obesity induced experimentally in human subjects mimics in several respects the changes observed in spontaneous obesity. These respects are (1) an increased level of basal insulin and increased insulin secretion following glucose stimulation, (2) impaired glucose tolerance, (3) insulin resistance as measured by glucose oxidation in adipocytes obtained by either of two experimental approaches, and (4) insulin resistance in muscle similar to that observed in spontaneous obesity.

As was pointed out earlier, diabetes is prob-

ably a heterogeneous collection of entities. Obesity is one factor which can bring out a genetic tendency toward diabetes. Obese patients show hyperplasia of the islets of Langerhans in the pancreas[126] and increased insulin secretion. Abnormalities in glucose tolerance are frequently observed in obese patients. The degree of abnormality appears to correlate better with the duration than with the magnitude of the obesity.[127] A person who has been overweight for a long period is more likely to have an abnormality in glucose tolerance than a person of the same weight who gained the weight rather acutely.

This suggests that exhaustion of the insulin secreting capacity occurs gradually, leading to diabetes mellitus. Just as diabetes can develop in obese patients with a long-standing problem, so there is convincing evidence that weight loss will lead to an improvement in glucose tolerance.[128] If, as appears to be the case, obesity increases the demand for insulin, then weight loss would be expected to diminish the demand for insulin and allow the pancreas to recuperate.

Lipid Metabolism, the Polyol Pathway and Vascular Complications

ROBERT H. FISER, MD*

MUCH IS KNOWN about carbohydrate metabolism and the metabolism of fat and protein, yet it is probable that a fuller understanding of the pathophysiology of diabetes and obesity will require a more thorough understanding in each of these fields and their interrelationships. In this discussion I will attempt to relate the known derangements in the metabolism of lipids and lipoproteins to abnormalities of the polyol pathway and how these interrelationships might affect the vascular complications of diabetes.

Lipid Physiology

A brief review of lipid physiology is in order. For a more detailed discussion of lipid metabolism and the transport of lipoprotein, the reader is referred to several recent review articles.[160-163]

Blood lipids—cholesterol, phospholipid and triglyceride—circulate in plasma bound to proteins. Proteins impart solubility to the otherwise insoluble lipid. Fat is transported in plasma as lipid-protein complexes or lipoproteins. Fatty acids circulate in plasma combined with albumin, with a slight amount transported within each of the lipoprotein classes.

Lipoproteins are complex macromolecules composed of varying proportions of lipid, carbohydrates and protein.[160-162] They can be most simply visualized as an inner core of lipid surrounded by a coating of phospholipid and protein. Binding of the lipid to the protein is weak enough to allow ready exchange of lipid among serum lipoproteins and tissue, yet strong enough to allow for separation by several physical and chemical techniques.[161]

Four lipoprotein classes are normally present in plasma. The characteristics of each group are shown in Table 9.[160] Methods for differentiation of these lipoproteins are based on either electrophoresis or ultracentrifugation. Lipoproteins have been separated into chylomicrons, very low density lipoproteins (VLDL or pre-beta), low density lipoprotein (LDL or beta) and high density lipoproteins (HDL or alpha). In brief, chylomicrons are the largest and lightest of the lipoproteins and remain at the origin after electrophoresis. Chylomicrons contain approximately 90 percent lipid and 2 percent protein, the lipid portion consisting mainly of tryglyceride, all of dietary or exogenous origin, with only small amounts of cholesterol and phospholipid. Chylomicrons are synthesized in the intestine cell wall and serve to transport dietary fat from the intestines to the peripheral tissues for utilization. Chylomicrons impart turbidity to plasma, and if the plasma is allow to stand they float to the top or form a creamy layer.

Very low density lipoproteins are the next smallest and lightest. VLDL contain 88 to 95 percent lipid and 5 to 12 percent protein. Fifty percent of the lipid portion is triglyceride. These lipoproteins remain uniformly distributed throughout the specimen after storage in the cold. VLDL transport triglycerides, primarily of hepatic or endogenous origin, that are synthesized from various precursors of free fatty acids and carbohydrate. In the absence of chylomicrons or during the fasting state this lipoprotein class correlates closely with triglyceride levels in plasma.[164]

Low density lipoprotein contains by weight approximately 50 percent cholesterol, 20 percent phospholipid, 10 percent triglyceride and 20 percent protein. Although the precise origin is un-

*Assistant Program Director, Clinical Study Center, Harbor General Hospital; Assistant Professor of Pediatrics, UCLA School of Medicine.